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Chapter 4

THE CONTROL OF CARDIAC OUTPUT DURING EXERCISE

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The concepts presented in Starling's famous Linacre lecture were perhaps some of the earliest, most significant contributions made in regard to the regulation of cardiac output.[21] He explained that the heart, in an isolated heart and lung preparation, had an inherent control system because the cardiac muscle responded similarly to skeletal muscle, i.e., as the end-diastolic volume increased, stretching the fibers, the muscle contracted more forcibly causing an increased ejection from the heart. When venous inflow increased, the end-diastolic volume increased and within a few beats the flow out equaled the flow in. By this mechanism it was postulated that because the venous return increases during exercise due to the additional pumping action of muscles and deeper respiratory movement, a distention of the ventricle takes place and an increase in stroke volume results.

With some modification Starling's concept was extended by Sarnoff in later investigations[17, 18, 20] which showed there was a relationship between the end-diastolic pressure and the stroke work of the ventricle and that not one curve but several existed. It was possible to move from one curve to another by injection of epinephrine and also by stimulation of the sympathetic nerves.

In these studies stroke work in grammeters was calculated by the following equation:

$$SW = \frac{(\text{mean arterial pressure} - \text{mean left atrial pressure}) \times \text{stroke volume}}{100}$$

and the recorded mean atrial pressure was assumed to be end-diastolic pressure. An effort was made to establish a relationship between other parameters such as right atrial pressure and left ventricular stroke work, atrial pressure and

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stroke volume, and atrial pressure and cardiac output. No consistent relationship was found to exist.

While it is evident from the experiments of Starling that the heart does have an inherent regulatory mechanism, the last series of experiments demonstrated that it can be modified by neural control. Further evidence seems to indicate that in the intact animal this basic control is so completely modified by other mechanisms that it appears to be almost nonexistent.

Roentgenkymograms at rest and exercise have shown that in the athlete the end-diastolic heart size gets smaller during exercise while at the same time the stroke volume may be markedly increased.[2] The increased stroke volume is apparently due to more complete emptying of the ventricle.

By measuring the ventricle diameter in an intact dog, Rushmer has confirmed these results.[15] During exercise the diastolic diameter decreases or remains at the same value as the resting control. The systolic diameter decreases slightly. When exercise is stopped, there is an increase in both diameters as the heart rate decreases. This type of response does not agree with the response that would be predicted by Starling's law, namely, that at rest the volume would be relatively small, during sleep a little smaller and during exercise the volumes of both diastole and systole would increase markedly and then decrease at the end of exercise. The only similar relationship which the diameter measurements showed was a decrease in ventricular diameter from the resting state to the sleeping state.

Rushmer also performed a series of experiments in which an effort was made to isolate the cause and effect of some of the parameters which affect cardiac output in an intact animal.[13, 16] After exercising a dog on a treadmill and obtaining a normal response, experiments were done on the same dog in an effort to simulate the responses of the dog during exercise. It was found that stimulation of the hypothalamic and diencephalic areas produced responses very similar to those of exercise both in heart rate change and in change of ventricular function. Because the diencephalon is probably a crossroads for nerve impulses coming from many portions of the cerebral cortex and other areas of the brain, it is possible that stimuli entering from the external sense organs and also impulses from the motor cortex which initiate movement in the skeletal muscle can initiate the appropriate cardiovascular and respiratory responses that occur during exercise.

The type of reasoning which states that the control of the cardiovascular responses during exercise is essentially originated from the higher centers of the brain allows some cause for question because it means that there is no closed-loop system controlling the response and the change is only modulated through the effect of baroreceptors and chemoreceptors. In examining some other control systems of the body, the changes seem to be directly related to need. Furthermore, it has been shown that the cardiac responses to exercise are closely related to the metabolic needs of the muscle, i.e., changes in oxygen uptake.

The fact that cardiac output is changed because of a changing need was demonstrated by experiments on dogs with the A-V node destroyed by electrocautery.[28] With an atrioventricular block thus produced the heart was driven at a desired rate by an external stimulator. As the dog exercised at 3 miles per hour on a treadmill the heart rate was varied from 80 beats per minute to 240 beats per minute. A plot of cardiac output vs. heart rate showed that the cardiac output remains reasonably constant for different heart rates. However, as soon as the treadmill speed was increased to 4 miles per hour, the cardiac output also

increased from 7 liters per minute to 12 liters per minute, demonstrating that as exercise or metabolism increased the cardiac output increased.

With the indication that cardiac output was under closed-loop control a series of experiments was conducted to see if the controlling factor could be determined.

Experiment 1 — Normal Responses

Mongrel dogs, weighing about 15 to 20 kg., were anesthetized with intravenous nembutal (30 mg./kg.) and a left thoracotomy was performed at the third interspace. An incision was made parallel to the phrenic nerve in the pericardium 1.5 cm. below the nerve. The root of the aorta was freed from the connective tissue, and the excess fat was carefully dissected away from the aorta exposing the circumference of the aorta for a distance of about 3 cm. from the point at which it emerges from the heart. After making sure the aorta was free of all connective tissue, a 400 c.p.s. gated sine wave electromagnetic flowmeter probe[8, 9] was placed around the aorta by partially collapsing the aorta and sliding the aorta through a slit in the side of the probe. A fine polyethylene tube was inserted through the carotid artery to the level of the arch for pressure measurement. The incisions were closed and the dog was allowed to recover for four to five days in order that the effects of the operation would be greatly diminished.

With the dog standing on the treadmill, the outputs from the flow probe and pressure transducers were connected to an analog computer. From the flow signal, f(t), and pressure transducer output, p(t), the following variables were calculated in the analog computer using an integrate track-and-hold circuit.[31]

Heart rate	$HR = \frac{1}{T}$ where T = period of one heart beat
Stroke volume	$SV = \int_0^T f(t)\,dt$
Cardiac output	$CO = HR \times SV$
Mean pressure	$\bar{P} = \frac{1}{T}\int_0^T p(t)\,dt$
Peripheral resistance	$R = \frac{\bar{P}}{CO}$

Two records showing typical responses to exercise are shown in Figure 4–1. The records are of two different dogs and show the differences that can be obtained from the same amount of exercise of 4 miles per hour on a treadmill inclined 15 degrees. Record A of Figure 4–1 shows a rather slow change in the variables as compared with those in record B. Defining time constant as though single lags exist, i.e., the time constant equals the time it takes for the variable to change 67 per cent of its maximum change, it is seen that the time constants of A are in the order of ten seconds and those of B are about two seconds. In both cases resistance has a shorter time constant than does heart rate or cardiac output. The change in heart rate with the onset of exercise is from 160 beats per minute to 215 beats per minute in A, while in B the change is from 120

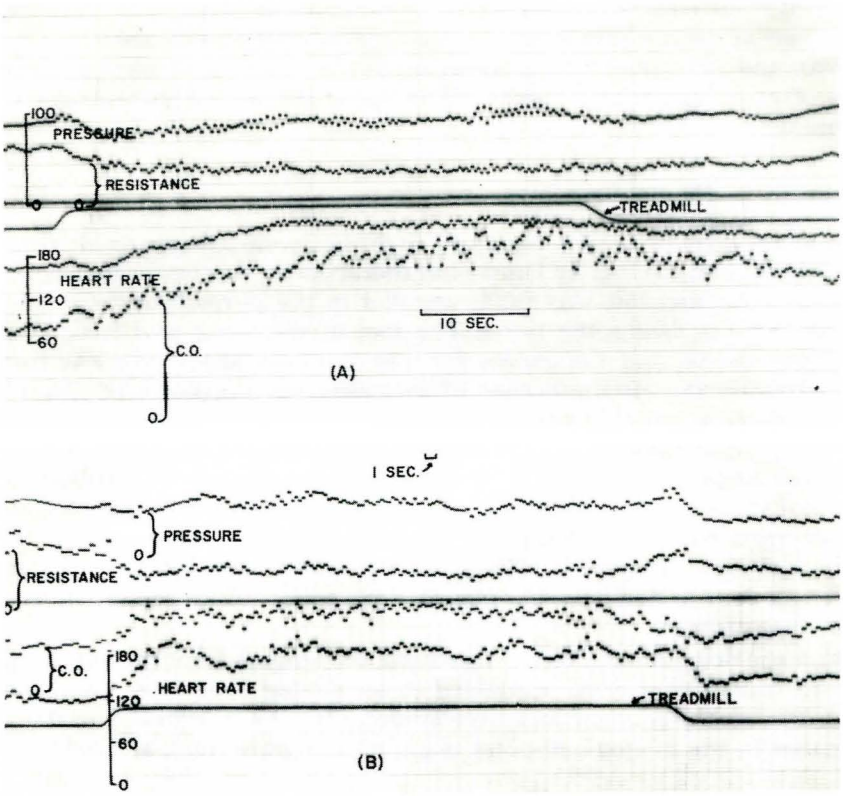

FIGURE 4–1. Records showing the normal response to exercise of two dogs calculated with the analog computer.

beats per minute to 192 beats per minute; this represents a change of 28 per cent and 60 per cent of resting values respectively. Perhaps the heart rate change in A was smaller because the resting rate was considerably above normal. It is interesting to note that while the heart rate changes were not the same, the changes in resistance and cardiac output were very similar with both records showing a drop of about 50 per cent in resistance and an increase of 75 per cent in cardiac output.

The overshoot seen in the heart rate of record B was observed in many dogs and was apparently caused by anticipation and excitement of the treadmill being turned on. This type of response is completely absent from A. In fact, in this record there is an unusual delay before the rise in heart rate. This delay was not observed in other dogs.

When the treadmill is turned off there is usually a rapid drop in heart rate, pressure and cardiac output with the time constant being about one second, as is shown in record B. This is probably caused by activation of the vagus

Table 4–1. Time Constants with Onset of Exercise (see Fig. 4–1).

	Heart Rate	*Cardiac Output*	*Resistance*
Record A	13 sec.	16 sec.	7.0 sec.
Record B	3.8 sec.	2.9 sec.	2.0 sec.

system which in turn causes a sudden decrease in heart rate. Since stroke volume, which is not shown on these records, usually changes only about 5 per cent, the drop in heart rate causes cardiac output to decrease, and because the resistance does not return to the resting value for 35 to 40 seconds after the end of exercise, the pressure also drops.

From the data just described, two factors indicate that changes in peripheral resistance influence cardiac output changes: (1) the drop in peripheral resistance is the most rapid, and (2) there appears to be a correlation between cardiac output and resistance independent of heart rate change.

Experiment 2—Controlled Constriction of Descending Aorta

The main purpose of this second series of experiments was to control the effective peripheral resistance by placing a constrictor around the descending aorta. To place a constrictor in the animal, the dog was again anesthetized and an incision was made through a left intercostal space just above the diaphragm. The constrictor was made from a balloon attached to a piece of the cloth. The cloth was wrapped around the aorta and tied snugly, with care being taken not to compress the aorta. Since the cloth would not distend, injection of air into the balloon compressed the aorta and increased the resistance to blood flow. After implantation of the constrictor the dog was allowed to recover for about seven days before experimentation.

With the analog computer making the calculations as described, the system used to control the peripheral resistance is shown in Figure 4–2. With the dog standing quietly on the treadmill, a value of peripheral resistance was calculated. This value of resistance became the reference voltage of the comparator in the integral control circuit. The output of this circuit was fed to an electropneumatic controller which maintained a constant pressure on its output for a given voltage on the input. The output of the controller was connected to the balloon constrictor which was around the descending aorta of the dog. As the dog exercised and the peripheral resistance started to drop, an error was introduced into the comparator and a voltage was applied to the pneumatic controller causing an increase in pressure in the balloon. The balloon com-

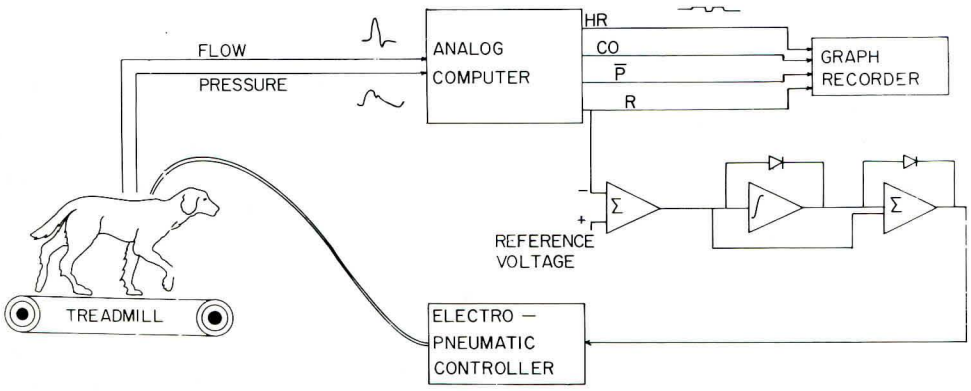

FIGURE 4–2. A diagram of the systems used to control peripheral resistance in a dog with a balloon constrictor on the descending aorta.

pressed the aorta against the cloth cuff and caused constriction. Through this means the peripheral resistance was essentially maintained at a constant value.

During each experiment of this series a normal response to exercise was obtained and then exercise runs were made with the controller activated. Figure 4–3 shows a typical exercise response with the treadmill at 4 miles per hour and an incline of 10 degrees. The top record shows the normal response and the bottom record shows the response with the controller activated.

First, considering the normal response of the dog without any control, the heart rate rose 120 per cent above the resting value within five seconds after the treadmill was turned on. The cardiac output increased to 70 per cent above its resting value and peripheral resistance fell to 45 per cent below its resting value. The mean aortic pressure had a small dip of 12 per cent, after which it rose 20 per cent above its resting value. The dog was exercised again at the same treadmill speed three minutes after the completion of the normal exercise run. This time, however, just prior to turning on the treadmill, the controller was turned on and resistance was maintained at a mean value equal to the normal resting resistance. Here, there is no marked increase of heart rate with the onset of exercise, although there is a slight increase as exercise continues. This amounts to about a 30 per cent increase over the resting value. There is the same slight increase in cardiac output as was observed in heart rate. The arterial pressure seems to increase the same amount in both cases.

From these results it appears that the drop in peripheral resistance is important in changing the heart rate and cardiac output at the onset of exercise.

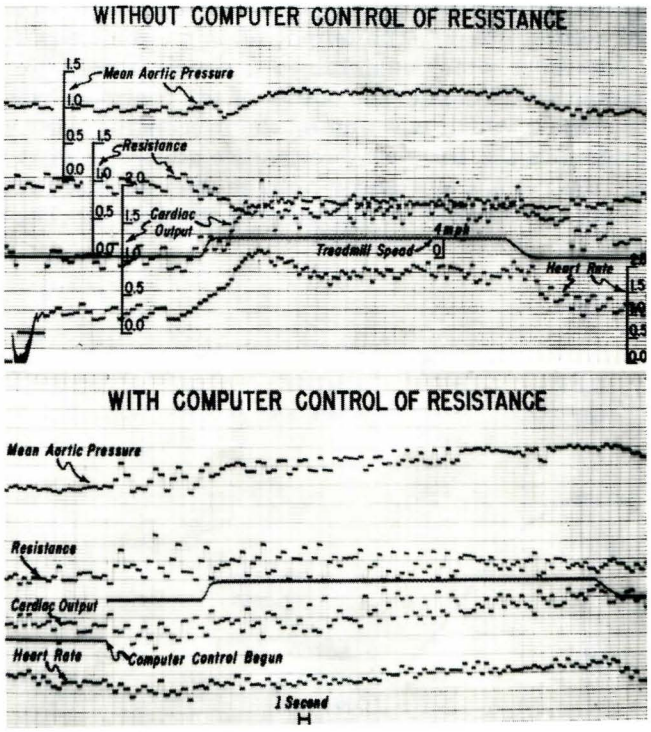

FIGURE 4–3. Two records showing the responses of a dog exercising at 4 miles per hour with and without resistance being controlled.

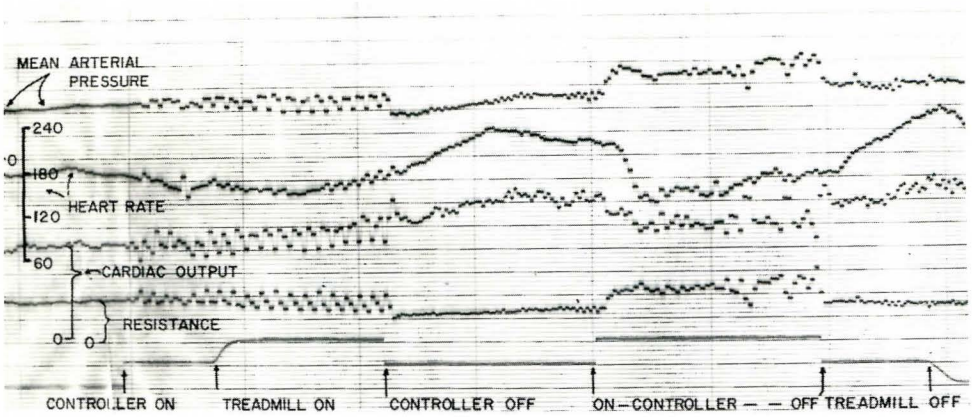

FIGURE 4–4. A record showing the effects of turning the resistance controller on and off during exercise.

If peripheral resistance is not allowed to drop, the marked changes in heart rate and cardiac output of exercise do not occur and exercise cannot be continued. When the dog ran at 4 m.p.h. or faster for a longer period of time (about one minute) with the constrictor applied, his back legs collapsed because there was not sufficient increase in blood flow to these limbs to support exercise.

In Figure 4–4 we see the effect of turning the controller on and off during exercise. The controller was first applied prior to turning the treadmill on. Here, as has just been described, with resistance held at normal levels, there is a small increase in cardiac output and in heart rate. When the controller is turned off while the dog is exercising, there is a sudden drop in resistance and pressure and an increase in heart rate from 180 to 235 beats per minute.

When the controller is applied again, raising the resistance back to its near normal value, there is a rise in pressure, a drop in heart rate to 140 beats per minute and also a drop in cardiac output. Turning the controller off once again the pressure and the peripheral resistance drop, the heart rate increases to 250 beats per minute and the cardiac output increases. The treadmill is turned off and a rather rapid decrease in heart rate to 220 beats per minute is observed as was shown in the first series of experiments.

In an effort to obtain a better understanding of the involvement of the baroreceptors and the central nervous system in this type of control, a third series of experiments was performed.

Experiment 3—Brachiocephalic Constrictor

In this set of experiments a more exact effect of the baroreceptors was considered by first denervating the aortic arch and then controlling the pressure in the carotid sinus by means of a constrictor on the brachiocephalic artery (Fig. 4–5). The pressure sensed by the intact baroreceptors then could be controlled by the constrictor. This maneuver, as in the preceding experiment, opens a reflex loop in the intact animal and the direct effect of carotid sinus baroreceptor stimulation can be observed.

With the outputs from the flow transducer, f(t), and pressure transducers, $P_{cs}(t)$ and p(t), connected to the computer and with the dog standing quietly on the treadmill, a step voltage was applied to the electropneumatic controller.

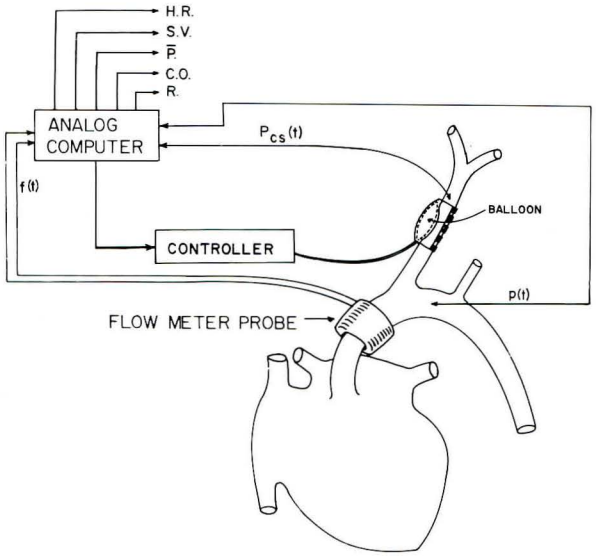

FIGURE 4–5. A diagram of the system used in the experiments when the brachiocephalic artery was constricted.

This increased the pressure in the balloon and constricted the brachiocephalic artery. The results of this constriction are shown in Figure 4–6.

When the constrictor was applied, the carotid sinus pressure dropped to about 50 per cent of its unconstricted value, and while in this record the pressure remained at this level, some dogs showed a gradual return to a value 25 per cent below the unconstricted value. This gradual return was probably brought about by the collateral circulation from the left vertebral artery. From this change in carotid sinus pressure the expected increase in heart rate oc-

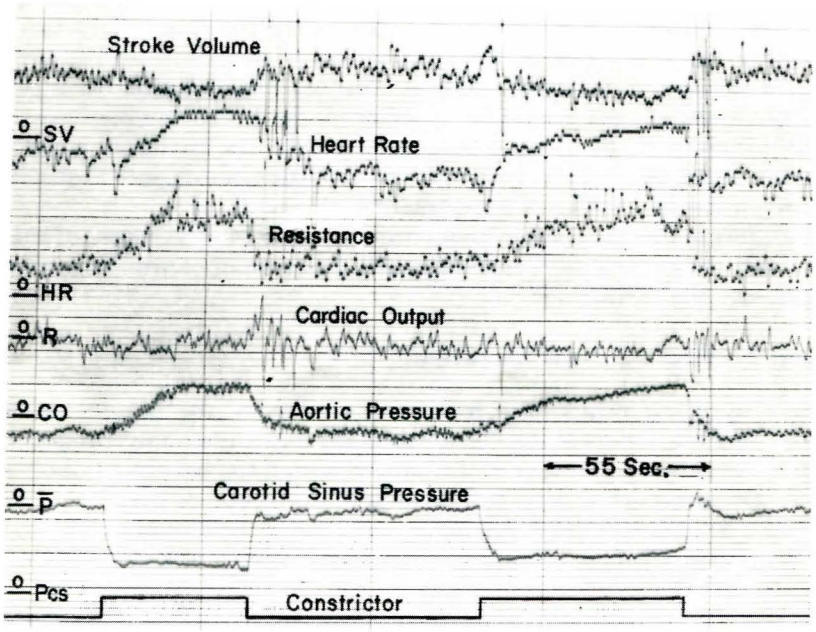

FIGURE 4–6. The response to constriction in the brachiocephalic artery with the aortic baroreceptors destroyed.

curred but cardiac output remained essentially constant. A rise of 80 per cent in mean aortic pressure was also observed. This change in pressure has a time constant four times longer than the time constant of the drop in carotid sinus pressure, indicating that the increase in pressure is due primarily to reflex sympathetic vasoconstriction and not to the occlusion of one of the major vessels.

Release of the constrictor allowed the increased pressure to be sensed by the baroreceptors, and a strong inhibitory reaction resulted. The heart rate dropped, and the aortic pressure returned rapidly to the unconstricted value.

The dog was then exercised on the treadmill at 4 miles per hour, and the constrictor was turned on and off during the exercise run. Table 4–2 gives the values obtained from one dog which showed a typical response. The values of stroke volume, heart rate, cardiac output, mean pressure and resistance are mean steady state values reached during each condition mentioned. All parameters have a value of 1.00 with the dog standing quietly on the treadmill.

In this dog there is a 17 per cent increase in stroke volume and a 36 per cent increase in heart rate during exercise. This gives a 60 per cent increase in cardiac output, two-thirds of which appears to be due to heart rate. However, when the constrictor is applied during exercise, an additional increase in heart rate of 57 per cent is obtained, but because the resistance is also increased due to the strong vasoconstriction action of the sympathetics, the stroke volume decreases 25 per cent causing the cardiac output to increase only 20 per cent. Thus, unless resistance is allowed to decrease or at least remain at the same value, the increase in heart rate has a small effect on cardiac output. A typical response of heart rate, cardiac output and carotid sinus pressure to brachiocephalic constriction during exercise is shown in Figure 4–7. Notice the agreement with the preceding explanation.

It appears that there are two ways to increase cardiac output during exercise, both of which are resistance dependent. Heart rate may increase because of the baroreceptor reflex, and stroke volume may change because of the resistance changes which occur and are reflected by the aortic pressure. From this explanation, the stroke volume mechanism appears to have dominating control.

Exercise affects the animal in two ways. One of these is an overall arousal of the animal, apparently initiated in the central nervous system. This arousal may reset the reference pressure level and thus account for the increase in pressure that was seen in Figure 4–3 under normal conditions. This effect can be demonstrated when the experimenter merely reaches to turn on the treadmill; while no actual exercise takes place, an increase in heart rate appears. This type of response could also account for the overshoot that is observed in Figure 4–3 in the heart rate. The other effect is essentially a vasodilatation in the

Table 4–2. Variable Values Obtained with Brachiocephalic Constriction at Rest and During Exercise.

Condition	*Stroke Volume*	*Heart Rate*	*Cardiac Output*	*Mean Pressure*	*Resistance*
Normal, resting	1.00	1.00	1.00	1.00	1.00
Constriction, resting	0.75	1.64	1.24	1.92	1.55
Normal, exercise	1.17	1.36	1.60	1.29	0.80
Constriction, exercise	0.92	1.93	1.80	2.10	1.17

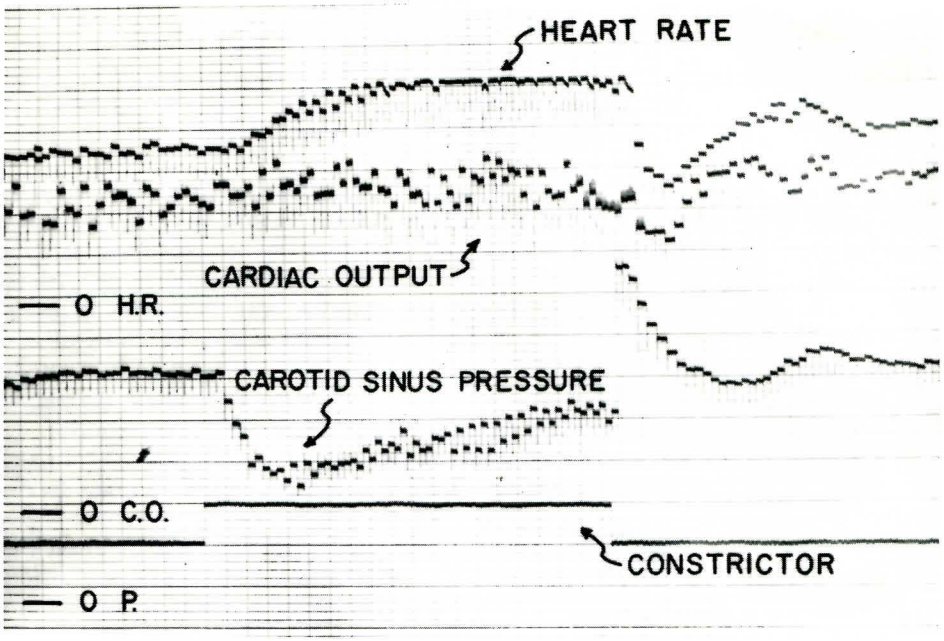

FIGURE 4–7. The effect of constricting the brachiocephalic artery during exercise with aortic baroreceptors destroyed.

skeletal muscle causing a drop in peripheral resistance and allowing more blood to flow through the exercising muscle.

With these ideas and the results of the experimental data in mind, the model diagrammed in Figure 4–8 was proposed. Since arterial pressure is a product of cardiac output and peripheral resistance, it is seen that if cardiac

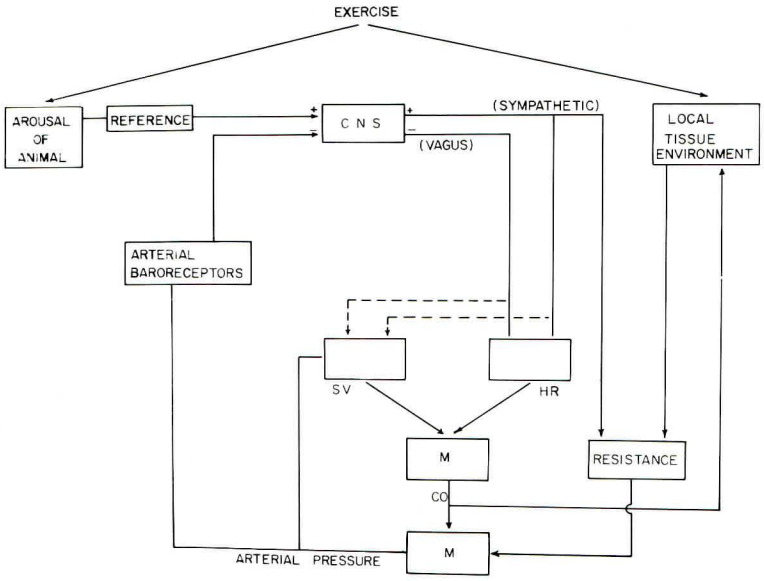

FIGURE 4–8. A block diagram of the proposed model for the control of cardiac output during exercise.

output momentarily remains at a constant value, the drop in peripheral resistance will cause a drop in arterial pressure. This drop in pressure is detected by the baroreceptors in the aortic arch and in the carotid sinus area, and a decrease in activity on the afferent nerves from these areas is sensed by the cardiovascular control center in the medulla. When this change in frequency is compared to a reference level, which has probably been modified by the arousal, an increase in frequency of firing in the sympathetics and a decrease in frequency of firing of the vagus nerve result. This increase in activity on the sympathetics increases heart rate and may affect stroke volume, but stroke volume is primarily determined by the direct mechanical impedance of the aorta. Since cardiac output is the product of stroke volume and heart rate, it is increased and arterial pressure returns to a near control value.

Analog Computer Model

To further justify the validity of the model of Figure 4–8 and to determine quantitatively the parameters involved in the system, the model was programmed for the analog computer. A description of the equations and considerations involved in the analog computer setup can best be obtained by considering the schematic diagram in Figure 4–9.

Little is known of the method by which the central nervous system detects

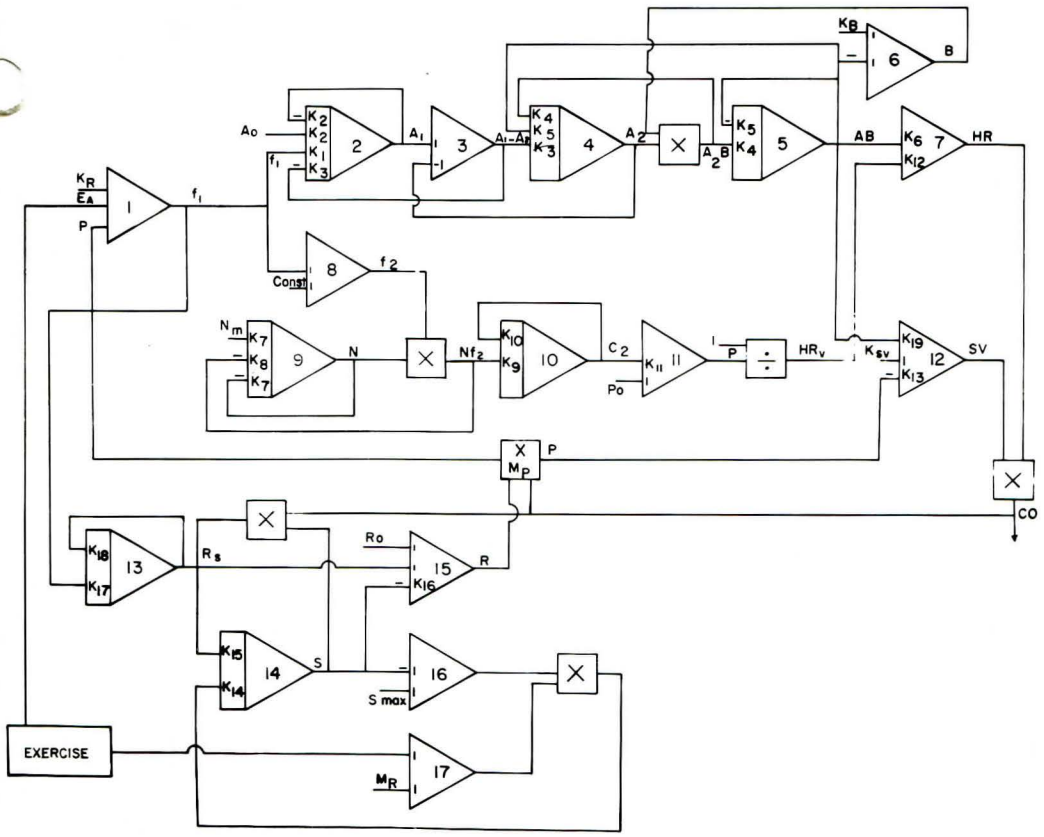

FIGURE 4–9. Analog computer schematic diagram for the simulation of control of cardiac output.

the change in frequency of firing of the baroreceptor nerves, but experiments seem to show that some type of comparator exists. For this reason, a summer was used and comparison was made between a reference level and pressure. Since exercise appears to have a direct effect on the central nervous system and may modify the reference level, a signal proportional to exercise was added.

The output of the summer is then the frequency present on the sympathetic (f_1) and vagus systems (f_2) with f_1 being proportional to the summer output and f_2 inversely proportional to the output. The equations and computer setup which describe the relationship of f_1 and f_2 to heart rate are those which Warner reported in 1962.[26] The total effect of these nerves on the heart rate was assumed to be the sum of the individual effects. From Warner's paper it is known that this is only a loose approximation, but it was used because the function describing the interaction of f_1 and f_2 is not known. Stroke volume is calculated from a constant no-load stroke volume which is modified by the mean arterial pressure and sympathetic activity. Since a quantitative relationship between stroke volume and frequency of firing of the sympathetics has not been described, it was assumed that the same diffusion process of norepinephrine as was used in the calculation of heart rate was present.

Since little quantitative information is known about the mechanism which causes vasodilatation during exercise, the time course of resistance during an exercise run was used as a guide in deriving an equation to be used in the analog model. This time course of resistance showed a rapid drop in resistance (two to ten seconds), with the onset of exercise and slow return at the end of exercise of about 40 seconds.

One accepted opinion for the cause of vasodilatation is a build-up of a metabolite having a local effect with no change being mediated through the nervous system. Accepting this concept, the following derivation was made. The concentration, S, of a metabolite is related to resistance,

$$R = R_1 - KS$$

where R_1 is the normal resting value of resistance and includes the effect of sympathetic action. The change in S is proportional to the formation of the metabolite and the rate at which it is destroyed,

$$\frac{dS}{dt} = K_1M - K_2S$$

where M is the metabolism of the metabolite and consists of two parts, resting metabolism, M_r, and working metabolism, M_w. K_1 is much larger than K_2 because of the fast drop and slow return of resistance. Since resistance reaches a certain value and will decrease no further, it was assumed that only a certain concentration of the metabolite, S_{max}, could be reached. K_1 is therefore a function of $(S_{max} - S)$. One of the factors affecting K_2 would be the washout of the metabolite, which would depend on cardiac output. Considering these factors, the equation for the change of S with respect to time becomes the following:

$$\frac{dS}{dt} = K_{14}\,(S_{max} - S)\,(M_r + M_w) - K_{15}CO \cdot S$$

To begin the model matching, the baroreceptor reflex was considered first by interrupting the feedback from the pressure multiplier, M_p, and driving the model with a carotid sinus pressure obtained during one of the brachiocephalic constriction experiments. The parameters of the model were adjusted until a match between the theoretical and experimental aortic pressures was obtained. Next, heart rate was considered and a good match was obtained. Stroke volume was matched next, and cardiac output and resistance were then determined.

With the parameters of the model approximately determined, the pressure multiplier output was reconnected, and treadmill speed was used to drive the model since it was assumed to be proportional to exercise. A match for resistance was obtained first, as it was the least sensitive to adjustment of parameters in the other parts of the model and seemed to be dependent on the time course and amplitude of the forcing function. A match for heart rate was then obtained followed by stroke volume. With the model predicting these three variables, the cardiac output and mean pressure were automatically determined. Using this procedure, the ability of the model to describe the experimental data is shown in Figure 4–10. The match appears satisfactory at the onset of exercise and throughout the run. The most obvious error occurs in the change of pressure at the end of exercise. However, closer observation shows that this error may exist because the resistance may rise too soon and cause the pressure to remain at a larger than correct value as cardiac output drops. Even more important, it is known, as was assumed in this model, that direct summation of the vagus and sympathetic effects on heart rate is only a rough approximation because moderate vagus stimulus will completely destroy any observed sympathetic action. In this case, the vagus response would not be as large as it should be and the HR and thus cardiac output would not decrease rapidly enough to cause the rapid drop in pressure.

This analog model provides a solution to the control of cardiac output. This solution is not unique, and as the model is used to predict the response to different types of stimulation, changes may be made. However, a basic model has been presented based on experiments which show that peripheral resistance is

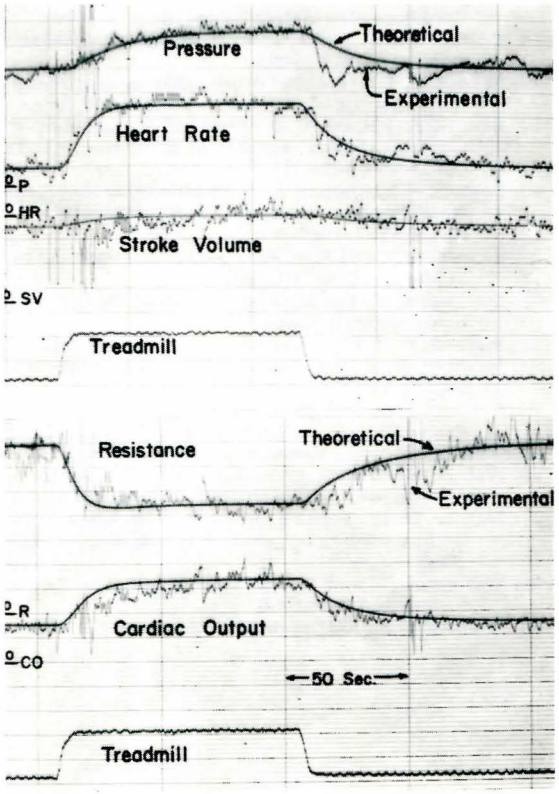

FIGURE 4–10. The prediction by the analog computer model of mean pressure, heart rate, stroke volume, resistance and cardiac output during exercise. The prediction is superimposed on curves obtained from experimental data.

an important factor in controlling cardiac output, both by its effect on the baroreceptor reflex and its direct mechanical effect on stroke volume.

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